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ALZHEIMER'S AND PERSPECTIVES FROM MEDICINAL PLANTS AS THERAPEUTICS: A REVIEW

ANNIE JESSICA TOPPO AND SHEELA CHANDRA*

Department of Bio-Engineering, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India- 835215

ABSTRACT

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in usually middle or late life period of an individual. There are upsurging evidences that oxidative stress is mostly responsible to the dementia. There are many drugs in the market recommended for dementia, which shows affect on diseased patients only up to minimal level, but after sometimes their suffering continues. Many drugs like Bryostatin 1, Crenezumab are there which shows promising results in clinical trials, but many shows failure after going through trials, few of them are Avagacestat, Ponezumab, etc. They also shows side effects like, indigestion, nausea, weight loss, loss of appetite and loss of strength which makes the case even worse. To rectify these activities of drugs or to avoid these, administration of secondary metabolites perhaps shows some satisfying results. Many ongoing researches on plant's secondary metabolites like curcumin, tocopherol which are already been commercialized, shows ability to cure amyloid and tau related problems which causes dementia. Regular consumption of these nutritive substances may prevent the effects of oxidative effect on cells which causes AD.

KEYWORDS: **Alzheimer's disease, Presenile, Secondary metabolites, Dementia, Oxidative stress , Amyloid**

SHEELA CHANDRA
Department of Bio-Engineering, Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India- 835215

***Corresponding author**

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INTRODUCTION

Alzheimer's disease is a neurodegenerative disease which is related to age in progressive manner, impeding memory and other brain operations[1]. The disease invades individual's memories, relationships and their persona, ability to care themselves and finally their life. In accordance to Alzheimer's Associations, Alzheimer's disease holds 6thrank in U.S.A having 5.4 million people suffering and counting. It is expecting that, the number of affected people will reach up to 106.8 million by 2050 worldwide[2]. Characteristics of Alzheimer's disease show advancement of arrears in more than one area of cognition, episodic memory, language, praxis and attention[3-4] Literature survey also reveal other symptoms regarding this disease like, impaired memory, distortion in functioning of cognition, alteration in behavior, in appropriation in social behavior, declination in functioning in language[5]. Clinical diagnosis of AD is depends on it's barring criteria which is only possible through necropsy[6]. It also based on patient's previous records and clinical assessment and neuropsychological appraisals[7-8]. In the context of diagnosis, the Positron Emission Tomography combined with various radiochemical endorsed to conjure up both amyloid plaques and neurofibrillary tangles, apart from this single photon emission computed tomography (SPECT) proves more advantageous in segregating the disorder from normal conditioned brain.Molecules in the serum or cerebrospinal fluid of diseased individual has been identified by using different parameters which helps in identifying the potential of the disease[7].For the pathogenesis of AD both environmental and genetic factors equally contribute[1]. More than a decade, it was already proposed that neurodegeneration in Alzheimer's disease is may be due to deposition of amyloid beta peptide (Aβ) in plaques in brain tissues[9]. Many literatures also proposed about some other causes which are responsible for AD, are mitochondrial dysfunction and oxidative stress[10-11].It is very interesting to know about amyloid beta theory and it is over production which brings on the evolution of secretase inhibitor, active and passive immunization approach. In spite of that, the drugs which are currently present in the market, like donepezil, memantine, revastagmine etc., are restricted in some extent[12]. Apart from synthetic medicines, herbal medicines in many cases proves to be more effective, due to its cultural eminence, consonance with human body, negligible side effects, due to all these reasons herbal medicines are upholder of many developing countries containing about 75-80% of population[3]. Many literature surveys approve that administration of herbal medicines shows improvement in learning memory in diseased patients[13-15].

CAUSATIVE AGENTS OF AD

Intensive cognitive studies has been carried out globally in different rating scales of patient's group, in this irresistible consequences of neuro degeneration has been observed, these are bizarre thinking and behavior[16-19]. Several literature shows that AD could also be caused by different reasons shown in table 1 like, mutation in the gene coding for amyloid peptide protein, excision of amyloid beta from haploprotein by β-APP cleaving enzyme (BACE)[20-26].

Table 1
Showing in the findings of causes of AD since 1994-2014

Year	Causes	References
1994	Synapse loss occur at an early stage of protein amyloid fibril deposition[10]	(10)
1998	tau phosphorylation and helical filaments assembly, due to inability of binding of ApoE4 to tau protein[6]	(6)
1999	Transfection of Asp2 into APP expressing cells results in an increase in the β- secretase activity[20]	(20)
2000	Hypothesis of 13 different aspects responsible for AD[27]	(27)
2001	Mutation in amyloid precursor protein increases protofibril formation and decrease in A β plasma level[28]	(28)
2002	Soluble oligomers of A β may be responsible for synaptic dysfunction in AD brains[28]	(28)
2003-2004	ApoE fragments generated in neurons in AD brains and can interact with tau and phosphorylated neurofilamants of high molecular weight resulting in large filamentous intracellular inclusions in neuronal cells[29,59]	(29, 58)
2005	Post translation modification of tau protein[30]	(30)
2006	Loss of Atg 7 (autophagy related 7), a gene essential for autophagy results limb clasping reflexes[26]	(26)
2007	Identified disease susceptible genes (e.g. ACE1, CHRNB2)[31]	(31)
2008	Oxidative stress[32]	(32)
2009	Decrease in cerebral blood flow[33]	(33)
2011	Hypothesis of autosomal mutation in presenillin1 (PSEN1 & PSEN2)[4]	(4)
2012	Autosomal dominant inheritance of genes amyloid precursor protein (APP) and presenillin (PSEN) genes[34]	(34)
2013	P73 haplosufficiency epitomize risk factor for tau hyperphosphoryration[35]	(35)

GLUTAMATE TRANSPORTER SYSTEM: POSSIBLE CAUSE OF AD

Glutamate excitory actions are negotiate by three types of receptors for NMDA (N-methyl-D-aspartate), kainite and quisqualate. The main astroglial glutamate transporter i.e. GLT-1 is oxidatively modified by 4-hydroxyl nonenal (HNE) when they are bind together. This is a lipid peroxidation product formed on the inferior parietal region of the brain of the individual suffering from neurodegenerative[36]. Abnormality in GLT-1 glutamate transporter system and momentous decrement of this system in cortex has been reported in diseased brain[4]. Addition of Aβ peptides in synaptosomes leads to lipid peroxidation[36-38]and increase the chances of binding of HNE to GLT-1[36], increases the amount of Aβ (1-42) which has affinity to bind with HNE, binds to GLT-1. In AD, when functioning of glutamate transport restricted, extraneuronal glutamate increases with subsequent inactivation of NMDA receptors and excitotoxic reactions involves accumulation of calcium results cell death with malfunctioning of tau protein expression shown in fig. I and II[39].

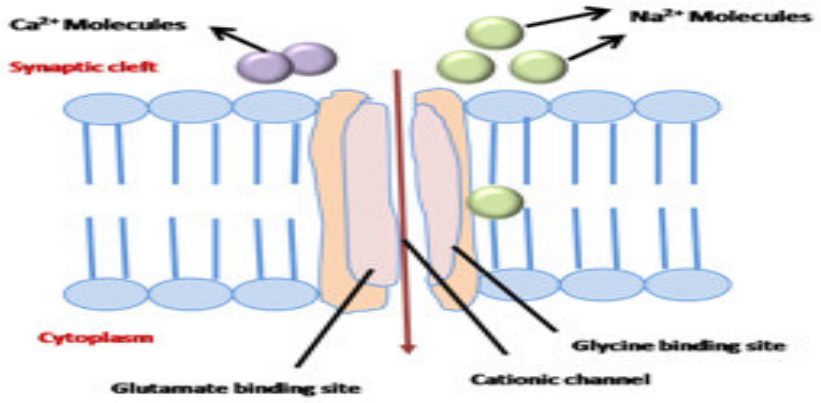

Figure I

Showing transportation of calcium ions (Ca^{2+}) and sodium ions (Na^{2+}) in cell and glutamate binding site[39].

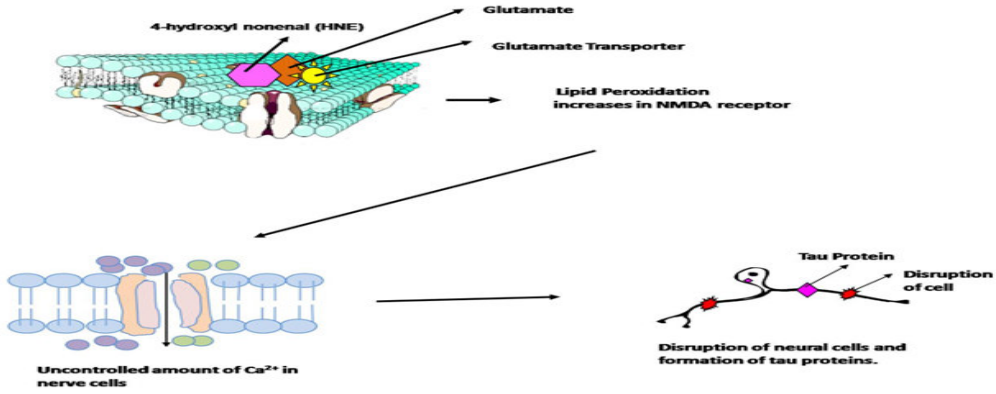

Figure II

Showing normally, glutamate attached to glutamate transporter, then it carried by N-methyl-aspartate receptor to nerve cells where it release control amount of calcium ions for functioning of nerve cells to carry message. but in diseased case, when glutamate attached to glutamate transporter, modified 4-hydroxyl nonenal got attached to glutamate transporter results to lipid peroxidation which increase the stimulation of N-methyl-aspartate receptor which release the uncontrolled amount of calcium ions which results in disruption of nerve cells formation of deformed tau protein results in amyloid beta plaque formation[39].

TAU PROTEIN MALFUNCTION

Distinctive feature of AD is accumulation of neurofibrillary tangles (NFTs) in the brain.The composition of NFTs involves paired helical filaments (PHFs) and straight (SFs) dissimilar to any normal neural fibrils.Tau protein is one of the major protein components of paired helical filament[40-41]. Tau is typically a cytosolic protein, to which obligate the stabilization of microtubule assembly from tubulin subunit. Biochemical dysfunction of tau in PHFs is due to abnormal hyperphosphorylation and other post translation modification, like glycosylation, ubiquitation, polyamination, nitration, proteolysis, in addition to being aggregated. Many literatures have demonstrated these perilous post transition of normal tau to toxic molecule which aggregate into PHFs/SFs and causes neurofibrillary degeneration in AD shown in fig. 3. The main cause for hereditary frontal temporal dementia is due to devising of tau mutation[30,42-44].

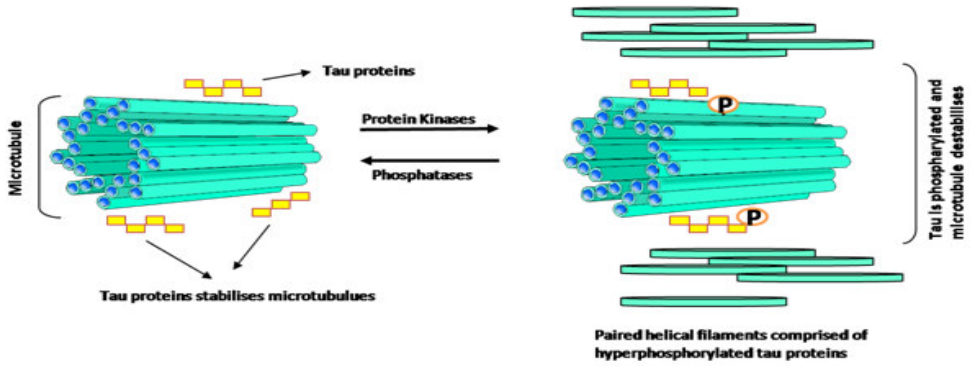

Figure III

Tau protein stabilizes microtubule, when it gets phosphorylated, results in destabilization of microtubule. Lastly, tau protein does not able to stabilize microtubule assembly from tubulin subunits results degeneration of neurofibres[30,42-44].

GENE MUTATION

Mutation may be the reason for AD; they could be APP, PS1 or PS2 which increases Aβ deposition, but still they shows no simple interdependence with age at which it first shows symptoms[6,45]. As a matter of fact, some presenillis in mutation escalate the Aβ metabolism which symptoms such as weakness which affects the lower periphery[22, 46-48] and the manifestation of "cotton wool" plaques, with early AD onset. However, the symptoms which distinguishes itself in due course, but not the bygone, is may be due elevation of apoE4 alleles[49]. They may associate to the point that the cell culture does not show any sufficient reflection about the complexity of Aβ prudence in brain, as the reason for phenotypic variations are not clear.

PREVALENCE

Millions of people worldwide have AD and other dementias shown in table 2. In 2013, around 44.4 million of people are suffering with dementia. This number will increment upto 75.6 million in 2030 and about 135.5 million in 2050. About 62% of individuals differing from dementia residing in developing countries, nevertheless by 2050 this will raise upto 71% shown in figure IV. Every year about 7.7 million new cases of dementia comes up, insinuating that there will be new case of dementia in every 4 seconds[50].

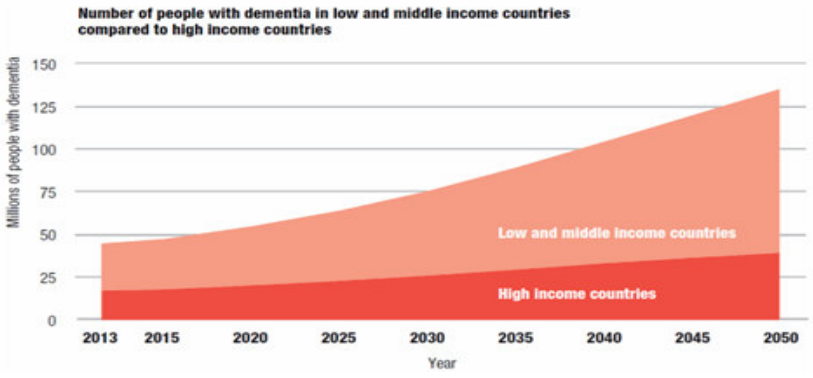

Figure IV

Showing number of individuals with dementia in middle and low economy countries compared to high economy countries

The numbers showing prevalent cases describe the magnitude of the burden of AD on the community and the health –care system, but it does not provide an estimate 5 million people aged 65 years and older and approximately 200,000individuals younger than 65 years who have younger onset of AD[7] (7).

DEVELOPMENT OF THERAPEUTICS FOR AD

The identification of major path physiological mechanism in for AD has led the discovery of molecular earmark for the development of specific drugs. Till date, there are about 200 pharmaceutical compounds and counting is present day undergoing 2 and 3 trials[51]. These pharmaceutical compound are divided into according to targets, like, anti-amyloid drugs and targeting other pathological pathways[23]. The resultant effect of extracellular Aβ oligomers and fibrillary forms synaptic dysfunction, affect exons and dendritic spines, leads to neuronal loss[52].Thus, pharmacological compounds that show promising altitude towards Aβ clearance or prevention against aggregation epitomize the strategy to delay the advancement of the pathological processes of disease[53]. From literatures, association of AD can be seen with loss of cholinergic

neurons in the basal forebrain. Cholinergic neurons have uniqueness in its metabolism that shows their contribution in their vulnerability in AD and aging. The neurons use choline for major two objectives: - a) phosphorylates into phosphocholine, further transformed into membrane phosphotidyl choline; b) acetylated into transmitter acetylcholine[40]. Wurtman has found that aging and AD shows association with decrement of choline uptake in synthesizing neurons. These results bring changes in membrane composition which supplementsthe conversion which supplements the conversion of APP to damaged amyloid[54].

Table 2
Showing compounds targeted to different causes for AD.

Compound	Company/institution	Target	Treatment	Current Phase	References
Bapineuzumab	Elan/Wyeth	Amyloid β deposition	Vaccine	Phase I ongoing[18]	(18)
Bryostatin 1	Blanchette Rockefeller Neurosciences Institute	Decreases Amyloid β	Monoclonal antibody	Clinical trial Phase II[23]	(23)
EHT-0202	ExonHit	GABA	α-secretaseactivator	Phase II clinical trial[18]	(18)
Solanezumab	Eli Lily	Amyloid β	monoclonal antibody	Phase III[23]	(23)
Ponezumab	Pfizer Inc.	Amyloid β	Monoclonal antibody	Interrupted at phase II[28]	(28)
Ganterezumab	Washington University School of Medicine	Amyloid β	Monoclonal antibody	Phase I[7]	(7)
Crenezumab	Roche	Amyloid β	Monoclonal antibody	Phase II[58]	(58)
Avagacestat	Bristol Meyers Squibb	gamma-secretase	Inhibitor	Interrupted at Phase II[7]	(7)
GRL-843[29]	Oklahoma Foundation Medical Research	BACE1	Inhibitor	Ongoing[55]	(55)
TAK-070[30]	Takda Pharmaceutical Company Limited	BACE1	Inhibitor	Clinical trial[58]	(58)
CHF5074	Chiesipharmaceutical	Inflammation	Nonsteroidantinflammatory agent	Clinical trial phase III[58]	(58)
Curcumin	Linkoeping University	Amyloid Beta	Aggregator	Ongoing[56]	(56)
PBT-2	Prana Biotechnology Ltd	Amyloid Beta	Inhibitor	Phase III[55]	(55)
Scyllo-cyclohexanehexol	Transition Therapeutics	Amyloid Beta	Inhibitor	Phase II clinical trials[55]	(Yan et al., 1999)
AVP923	Alzheimer's disease education and referral centre	NMDA receptor Antagonist	Inhibitor	Phase II clinical trial[55]	(55)
Donepezil	Eisai Company Inc. and Pfizer	AchE	Inhibitor	Approved for all stages[50]	(50)
Galantamine	Janssen Pharmaceticals	AchE	Inhibitor	Approved for Mild to moderate[50]	(50)
Memantine	H. Lundback	N-metyl-D-aspartate receptor	Inhibitor	Approved for Moderate to severe[50]	(50)
Rivastigmine	Actavis Inc.	AchE	Inhibitor	Approved for Mild to moderate[50]	(50)
Tacrine	Parke Davis of Morris Plain, New Jersey, Warner Labert Company.	AchE	Inhibitor	Mild to moderate[50]	(50)

When there was no cure of AD, US Food & Administration (FAD) approved five drugs to treat its symptoms. Tacrine is the first cholinesterase inhibitors was approved in 1993 shown in table 3.

ANTI-ACETYLCHOLINESTERASE

Anti-acetylcholinesterase are group of drugs which are prescribes to cure symptoms related to memory, language, thinking, judgment and other thought relates functions.

MODE OF ACTION OF ACETYLCHOLINESTERASE

In diseased condition, cells that produce and use acetylcholine, got damaged which reduces the amount of carrying messages shown in figure V and VI.The disintegration of acetylcholine by hindered the activity of acetylcholinesterase. For compensation of loss of functioning brain cells, these drugs help to maintain the acetylcholine levels. For example: galantamine one of the anti AChE drugs which revitalize the release of acetylcholine and build up many messages receiving nerve cells. Blockage of activation of another enzyme which is responsible for breakdown of acetylcholine is done by rivastigimine[50].

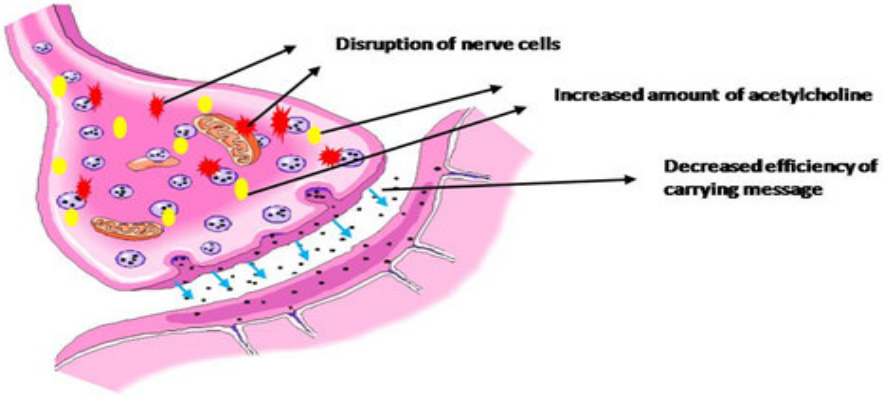

Figure V
Showing, in diseased case, nerve cells got disrupted due to which increased amount of acetylcholine is produced which reduces the amount available to carry message through nerve cells[50]

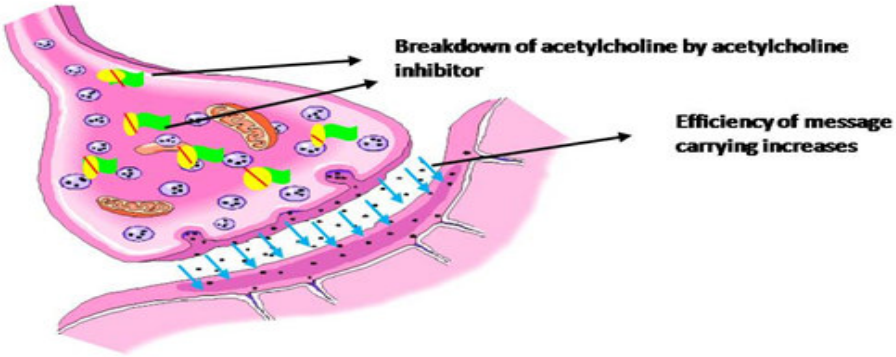

Figure VI
Showing, when acetylcholine inhibitor administered there will be breakdown of acetylcholine and hence there will no damage in nerve cells[50]

N-METYL-D-ASPARTATE RECEPTOR ANTAGONIST TYPE DRUG

Memantine is one of the first discovered by drug for NMDA antagonist who is recommended for improving memory, attention, reason, language and capability to carry out, simple tasks. From moderate to severe stage, memantine has ability to treat AD, but memantine was refused by FDA for approval for treatment of mild Alzheimer's.

MODE OF ACTION OF N-METYL-D-ASPARTATE RECEPTOR ANTAGONIST TYPE DRUG

NMDA drugs mainly control the regulation of activity of glutamate.The calcium ameliorates to create, chemical domain which is required for storing of information. These amounts of calcium are controlled in nerve by glutamate which participates in learning and memory by activating NMDA receptor. In diseased case, overstimulation of NMDA receptors allow enormous amount of calcium into nerve cells, that results to cessation of cells. To prevent this condition of cells, memantine partially blocks the NMDA receptors shown in figure VII(7).Scientists are still unable to understand the correct pathophysiology and mechanism of disease and its progression. Thus the selection of viable and effective targets for new medicines becomes very difficult. The development of *in vivo* models for AD is still a barrier in preclinical testing limiting the development of new entities.The unavailability of non-invasive biomarker delays the diagnosis of disease and its progression, makes detectability challenging in patients. This leads to long and expensive clinical trials[50].

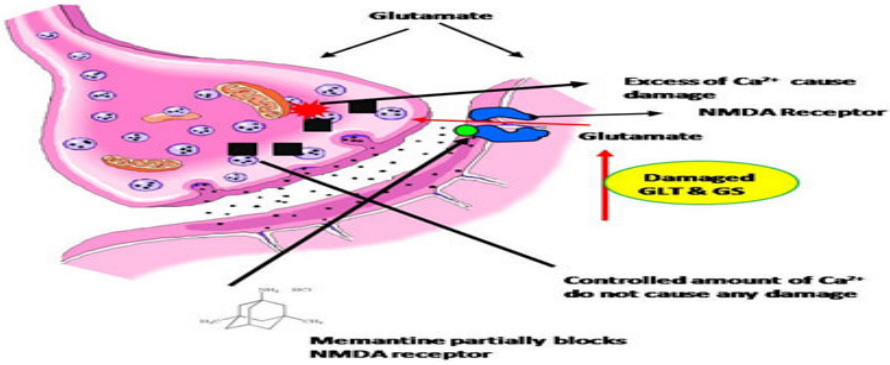

Figure VII

Showing, action of memantine against cell disruption which later form AD. In this we can see glutamate which is already present in nerve cells, transported through glutamate transport system (GLT & GS), control the transport of calcium in nerve cell, if the transporter system got damaged then NMDA receptor will not able to control the amount of calcium in nerve cells which cause insertion of excessive amount of calcium in cells results to disruption. When memantine administered, it protect the cells by antagonizing surfeit amount of molecules of glutamate, produces by preventing it in some extent in the NMDA receptor, hence cell will not disrupt[50].

Table 3

Showing possible side effects of drugs

Drugs	Common side effects
Donepezil	nausea, muscle cramps, unusual tiredness or weakness loss of appetite, diarrhea, vomiting
Galantamine	weight loss, loss of appetite, dizziness, diarrhea, vomiting, nausea
Memantine	abnormal laboratory test results,balanceproblems,breathingdifficulties,constipation,feelingdizzy,headaches,hypersensitivityreactions,raised blood pressure. Sleepiness.
Rivastigmine	weight loss, vomiting, nausea, loss of strength, loss of appetite, indigestion, diarrhea.
Tacrine	Clumsiness or unsteadiness, Diarrhea,loss of appetite,nausea,vomiting
Bapineuzumab	Vasogenicoedema
Bryostatin 1	nausea, fatigue, headache, vomiting, anorexia, anaemia, lymphopenia.
LY450139 Semagacestat	decrement of lymphocytes in spleen and thymus, hence change in immune system can be observed
PBT-2	Headache, dizziness, somnolence
AVP923	Behavioral problems

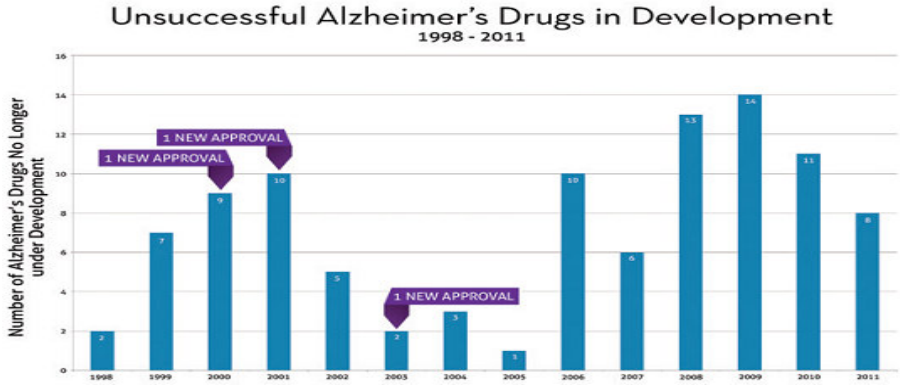

Figure VIII

Ineffective attempts, since 1998, to develop more adequate drugs which will combat with this disease[58].

An ongoing research has been carrying out by biopharmaceutical research to find new treatment which have potential to treat or slowdown or prevent AD. Nonetheless, the highway from primitive investigation to new drug treatments is intensive with numerous setbacks. As number of scrutinization regarding AD has failed to gasp patients every year shown in figure VIII. For every failure we have to subsidize new path. (50, 57).

PLANT SECONDARY METABOLITES AND ALZHEIMER'S DISEASE: CURRENT SCENARIO

In plant physiology, secondary metabolites playa very important role like, pigmentation, resistivity to pathogens, growth astringency and bitterness of plant. Several plants have free radical scavenging property, which are present in the form carotenoids and flavonoids. Regular consumption of these nutritive substances may have beneficial effects. Many reports also support that, the plants having antioxidant property, helps in prevention from nocuous effect of oxidative stress on signal transduction and nerve growth factors in rats. They also reduce the effect of malfunctioning motor behavior in nerves. All these experiments, shows beneficial effect or capability of plants to cure neuronal disease but these are not directly related to AD[58]. Amongst all secondary metabolites, heterogenic group of benzo-ç-pyron derivative, which is known as flavonoids abundantly found in food products and beverages, mainly from fruits and vegetables[59] shown in table 5. There are other metabolites like, vitamin E (tocopherol), vitamin C (ascorbic acid), vitamin D (calciferol), isoflavonoid type, phytoestrogens, fatty acids, influences membrane function in many ways. Even in cancer, these metabolites attune the activity of membrane enzymes and receptors. The various protective affects due to dietary components has also taken as consideration because it can implicated on DNA damage in neurodegeneration, malignant growth to cancer[60].

FLAVONOIDS

Flavonoids consist of two aromatic rings which are bound together by three carbon atoms that form an oxygenated heterocycle[61], divided into 6 classes: flavonols, flavones, anthocyanins and isoflavones. Catechins, quercetin and myricetin etc., are most common flavonoids[6]. Reveratrol, shows beneficial effect when it is consumed in equitable amount of red wine, it scavenges O2- and OH- invitro and lipid hydroperoxyl free radicals in case of dementia. Against neuroprotection the fruits and vegetables are invaluable, by influencing and modulating several cellular processes such as signaling, proliferation, apoptosis, redox balance and differentiation. The ability of these flavonoids to block TNF-α-induced CAM (cell adhesion molecules) expression could be due to their antioxidant properties63-65. Glutamate decreases the intracellular level of GSH by inhibiting the uptake of cystein which is necessary for GSH production, in addition quercetin and fisetin increase GSH levels in HT-22 cells[66-67].*Alcea pallida* shows promising results on free radical scavenging activity, which can be used for neurodegenerative disorders[68] .

SAPONINS

Saponins mainly contains sugar moiety which consists of galactose, glucose, glucoronic acid, xylose, rhamnosepr methylpentose, which is glycisidically linked to hydrophobic aglycone (sapogenin) which may be triterpenoid and steroid in nature. Activaion of mGluR8 in pilocarpine instigated epileptic rats has been reported to have anticonvulsant[69-72] mGluR8 gene expression play an important role in the pathophysiology of pilocarpine induced temporal lobe epilepsy in rats and B. monneri extracts shows a regulatory effect on mGluR8 gene expression in epilepsy[73-74]. *Anemarrhenaasphodeloides* mitigate learning deficits caused by brain damage and aging in rodent[75-77]. Components isolated from AA are sarsasapogenin and timosaponin BII enhanced learning and memory in amyloid β peptide (25-35) - or scopolamine induced dementia in rats[77]. Some species of Thymus contains both terpenes and polyphenols possess antioxidant properties with free radical scavenging activity, inhibiting lipid peroxidation and also exhibited anti-AchE activity[78].

ALKALOID

Rutaecarpine (Ru) is one of the alkaloid (quinazolinocarboline) isolated from *Evodiarutaecarpas*. It possesses a wide spectrum of pharmacological activities, like vasodilatation, anti-inflammation, antithrombosis[79-80]. In some literatures, it has been found that, the modification in the general structure of AChE and AChE inhibitors by including two components separated by a spacer group with compatible length, with aromatic ring binding with the PAS of AChE and with side chain terminal amino group interacting with catalytic site of AChE. By doing all these modification, rutaecarpine could improve AChE inhibitory activity based on docking studies[81]. Black Tea (*Camellia sinensis*) manifest about 78% of world population consumed tea and acquire neuroprotective properties under conditions like Parkinson's disease, ischemia and hypoxia.It was also found that harmine seeds of *Peganumharmala* is sequentially penetrating blood brain barrier inhibiting some early response genes.

Table 4
Showing action of different secondary metabolites and their action on AD

Plant	Secondary metabolites	Protective action	References
Citrus fruits	Vitamins C	Modulation of the activity of membrane enzyme[60]	(60)
Gingko biloba	EGb 761	Improve cognitive functions, protect against toxicity induced by Aβ- derived peptides on hippocampal cells[82]	(82)
Tea	Epicatechin	Against neuronal cell death due to oxidative stress[83]	(83)
Tea	Catechin polyphenols	Scavenging of radicals, activation of survival genes, iron chelating, cell signaling. Mitochondrion functioning[21]	(21)
Turmeric	Curcumin	Antioxidant properties, inhibit certain signal	(21)

		transduction pathways[21]	
Gingko biloba	EGb 761	Inhibition of Aβ oligomerization[82]	(82)
Bacopamonneri	Polyphenols	Antioxidant, anti inflammatory[21]	(21)
Green Tea	Catechin& 30-o-methyl-Epicatechin	Against oxidative damage, activation/ phosphorylation of signaling proteins for pro-survival pathways[83].	(83)
Saffron	Saffron extract	Antioxidant anti-amyloidgenic activity[13]	(13)
Walnut	Walnut extract	Reducing generation of free radicals, inhibiting membrane damage and DNA damage[6]	(6)
Blueberry, cocoa	Blueberry, cocoa extract	Interactions with ERK signaling pathway, Antioxidant, anti-inflammatory[85]	(85)
Coffee	Di- caffeoylquinic acid	Acetyl cholinesterase inhibitory activity[21]	(21)
Dispacusasper wall.	Akebiasaponin D	Protects P12 cells[86]	(86)
Isodonjaponicas	CBNUO6	Inhibition of NF-κB signaling pathway[87]	(87)
Fritillariaebeiensis	Labdanediterpenes	Against MPP^+induced neuronal cell death	(83)
Pepper	Piperine	Decrease peroxidation and acetylcholinesterase[88]	(88)
Tripterygiumwilfordii	Celastrol	Suppression of NF-κB pathway[42]	(42)
Aspergillusterrus	Isoterreulactone	Inhibit Acetylcholinesterase[28]	(28)
Vitamin E rich food	Vitamin E	Prevents lipid peroxidation[43]	(43)
Trifolium pretense L. *Spantholobussuberectus*, *Astragalusmongholicus Bunge*	Formononetin	Inhibit neuronl damage from NMDA exocitoxicity	(88)
Ceylon cinnamon	Cinnamonumzeylanicum	Anti tau[89]	(89)
Mulberry	Hygroxylstilbene	Pretreatment of SH-SY5Y cells[90]	(90)
Strawberry	Antioxidant polyphenols	PC12 cells[21]	(21)
Pomegranate	Phenolic antioxidant ellagic acid	SH-SY5Y cells[21]	(21)
Grape seed	Phenolic antioxidants and pro-anthocyanidins, Resveratrol	NF-κB,inflammation and oxidative stress[21]	(21)
Pappaya	β- carotene	bax/bcl-2 sensitive pathway, SH-SY5Y cells[90].	(90)
Apple	S-adenosylmethionine	AChE level, expression of presenilin-1[90]	(90)
Green Tea	Epigallocatechingallate (EGCG)	Activity of protein kinase C, proteolytic processing of amyloid precursor protein, lipid peroxidation, Bax gene, NF-κB levels[90]	(90)
Coffee	Caffeine	c-FOS, transcription activating factors, presenilin-1, b secretase[90].	(90)
CatharanthusRoseus	Caffeoylquinic acid	AChE[90]	(90)
Walnut	Ellagic acid	PC12 cell lines[21]	(21)
Saffron	Crocin	PC12 cells[21]	(21)
Curcuma longa	Curcumin	Heat shock proteins[21]	(21)
Pepper	Piperine	lipid peroxidation and AChE activity[21]	(21)
Cinnamon	Cinnamaldehyde, eugenol, cinnamyl acetate, and cinnamyl alcohol	cross the blood brain barrier (need to explore)[21]	(21)
Ginger	Bisabolene, zingiberene, and monoterpenes	AChE inhibitory activity, lipid peroxidation[21]	(21)
Ginkgobiloba	EGb761	ROS level, SH-SY5Y Cells[21]	(21)
Poncirus Trifoliate	Methoxsalen	AChE inhibition[21]	(21)
Salvia Officinalis		AChE inhibition[21]	(21)
ScrophulariaBuergeriana	KD501	AChE inhibition[21]	(21)
Salvia Officinalis		AChE inhibition[21]	(21)
HuperziaSerrata	Huperzine A	AChE inhibition, Bax and p53 genes, PC12 cells[21]	(21)
BacopaMonnieri	Brehmine, herpestine, nicotineandsaponin	AChE inhibition[21]	(21)
PaeoniaSuffruticosa	1,2,3,4,6-penta-O-galloyl-b-D-glucopyranose	SH-SY5Y Cells[21]	(21)
UncariaRhynchophylla	Oxindole and indole alkaloids	Ab fibrillation[21]	(21)
RosmarinusOfficinalis	Carnosol and carnosic acid	Keap1/Nrf2 pathway[21]	(21)
Galanthusworonowii	Galanthamine	AChE inhibition[21]	(21)
Magnolia Officinalis	4-O-methylhonokiol	AChE inhibition[21]	(21)
CoriandrumSativum	Flavonoid glycosides, caffenic acid	AChE inhibition[21]	(21)

CONCLUSION AND FUTURE PROSPECTS

Till date, many hypotheses were proposed to analyze the main causative agent for AD. In 1992 amyloid β cascade hypothesis was first proposed, assuming that β amyloid would be the suspect initiating pathogenesis of dementia. Hence, a series of exploration has been done and intensively focused on physiological and pathological processes. The enzymes responsible for cleavage of the presumably pathogenic amyloid beta from its precursor are: γ-secretase and BACE-1. Similarly, all of these many more causative agents have been found like oxidative stress, mutation in the gene coding amyloid peptide protein For all these causes many synthetic drugs are available in market like dopenezil, memantine, tacrine but the major setbacks of all were their side effects. In the junction of drug development using different models man drugs are in the track of validation. Due to this many drugs related to plant secondary metabolites come into interest to many researchers like, *Gingko biloba*, vitamin E, curcumin which are already commercialized. Regular consumption of these nutritive substances may prevent the effects of oxidative effect of cells which causes AD. So, for future, it really required it really required to get into department of disease proceedings and understand modification of AD, for this procedure, we need to know some specific answers of question like:

A) Which type of patients to be treated?
B) About the medication, which type for it is used for? How long will be these trials or medication goes?
C) Duration of medications and its trials?

Last but not the least, biological measures prove to be better tool to understand the outcomes of the trials, especially in clinical trials, to understand and measure the efficacy of drug.

CONFLICT OF INTEREST

Conflict of interest declared none.

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